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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1653	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/701,947	ALTMAN, ELLIOT
Examiner	**Art Unit**
Samuel W Liu	1653

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Paper NOs. 9 and 18* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 61-122* is/are pending in the application.

4a) Of the above claim(s) *61-88,98-103 and 106-119* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *89-97,104,105 and 120-122* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14 & 15* .
4)☐ Interview Summary (PTO-413) Paper No(s) _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Applicants' preamendment filed 7 May 2001 26 (Paper No. 9) as to amendment of claim 1, cancellation claims 2-60 and addition of claim 61-119, and the current amendment as to addition of new claims 120-122 filed May 6, 2003 (Paper No. 18) have been entered. Also, applicant's request for extension of time of one month filed 1 October 2002 (Paper No. 11) has been entered.

Election/Restrictions

Applicant's election of Group II, claims 89-97, 104 and 105, filed May 6, 2003 (Paper No. 18) and filed 11 March 2003 (Paper No. 17) is acknowledged. Applicant's election with traverse of Group II, claims 89-97, 104 and 105 in Paper No. 17 is acknowledged. The traversal is on the ground(s) that the invention as claimed can be examined without undue burden. This is not found persuasive because Undue burden is not an issue under 35 USC 371. Undue burden, however, is demonstrated by separate classification and search. For example, the Group I claims are classified and search in class 435, subclass 7.1 whereas the Group II claims (elected) are searched in class 530, subclass 300'. Thus, burden is shown. The requirement is still deemed proper and is therefore made FINAL.

Therefore, elected claims 89-97, 104 –105 and new claims 120-122 which are directed are under examination to the extent that they are drawn to the elected invention. Claims 61-88, 98-103 and 106-119 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Priority

Applicant's claim for the benefit of U.S. Provisional Application No. 60014013, filed 13 October 1998 under 35 U.S.C. 119 (e) is acknowledged.

Objection to Specification/Claims

The disclosure is objected to because of the following informalities:

(1) It appears that this application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

(2) In page 35, line 15, "PCR" should be spelled out for the first instance of use. See also page 45, line 1, "CAP", and page 61, line 15 "ori".

(3) In page 43, line 4, "$5OD_{550}$" is need to be clarified because this phrase does not unambiguously identify the cell equivalents to which the phrase precedes.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. §101 states:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 89-97, 104-15 and 120122 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

Claim 89 and dependent claims thereof, claims 104-105 and 120-122, as written, as written, do not distinguish the claimed peptides or polypeptides from naturally existing products. The claims do not particularly point out any differences indicating the hand of man. In the

absence of the hand of man, the claimed products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). Note that naturally-occurring antimicrobial peptide, termed Prophl (see column 4, line 35, and Figure 3 of US Pat. No. 5633229), has the stabilizing group "Xaa-Pro-Pro" as set forth in the application claim 120, for example. The claims should be amended to indicate the hand of man, *e.g.*, by insertion of "isolated" or "synthesized" as disclosed on pages 10-12, and pages 48-58 of Example II.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 89-97, 104 –105 and 120-122 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 89 recites "stabilizing group" is unclear as to whether or not the "stabilizing" refers to stabilizing a protein conformation or stabilizing chemical structure by preventing the protein from hydrolysis or protein degradation, or, stabilizing bioactivity of the protein. See also claims 91-92, 104-105 and 120-122.

The dependent claims are also rejected.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 89 and 97 are rejected under 35 U.S.C. 102(b) as being anticipated by Vanhoof G. et al. (*FASEB J.* (1995) 9, 736-744).

Vanhoof et al. teach bioactive neuropeptides, which hinder proteolysis and has stabilized bioactivity. One of them, Neuropeptide Y sequence has a "stabilizing" group "Tyr-Pro" at the N-terminus and a "Pro-Ala" at the C-terminus of Neuropeptide Y (see Table 4 and page 742, the right column, the second paragraph), which meets the limitation set forth in claim 89.

Neuropeptide Y agonists are useful in treatment of anorexia, epilepsy, anxiety, depression, hypertension and heart failure. Thus, Vanhoof et al. meets the claim 97 criteria as neuropeptide Y is used as a therapeutic agent.

Therefore, Vanhoof et al. anticipate claims 89 and 97 of the instant application.

Claims 89, 91, 96-97 and 120 are rejected under 35 U.S.C. 102 (a) as being anticipated by Kokryakov, V. N. et al. (US Pat. No. 5804553) which teaches a bioactive peptide: FPPPNFPGPR (see the fragment consisting of amino acid residues 12-21 SEQ ID NO:1 shown in column 14, lines 62-64); the structural feature, i.e., plurality of praline at N- and C-termini of the peptide meets limitation of the application claim 1, which anticipates claim 89.

The peptide is an antibiotic peptide (see the patent title; the patent claims 1-4; Table 4 data; and Figure 4 at and columns 3-4). This meets the limitation of claims 96, 97 and 120 which are anticipated.

The bioactive peptide: FPPPNFPGPPFPPPIFPGPWFPPPPPFRPPPFGPPR (see SEQ ID NO:9 at columns 21-22) possesses the structural characteristic with plurality of proline at N- and C-termini of the peptide comprising the motif "Xaa-Pro-Pro" at the N-terminus and "Pro-Pro-Xaa" at the C-terminus of the peptide, which meets the limitation set forth in the application claims 89 and 91.

Claims 89-90, 92 and 104 are rejected under 35 U.S.C. 102 (e) as being anticipated by Hanafusa, Hi. et al. (US Pat. No. 5888763), which discloses a bioactive peptide

"PPPALPPKKN" (see SEQ ID NO:26, column 5 and Figure 8B) having an N-terminal proline residue in comparison with the consensus sequence "PPALPPKKN"(SEQ ID NO:27, column 5 and Figure 8B); thus, the reference meets the limitation set forth in claim 89 "stabilizing group is selected from the group consisting of Pro-, pro, Pro-Pro-, Xaa-Pro- and Xaa-Pro-Pro-". The peptide is fused to a small stable protein, i.e., glutathione sulfotransferase (GST). Therefore, Hanafusa teaching anticipates claims 89-90 and 92 of the instant application. The fusion partner protein serves as a substrate for proteolytic cleavage (e.g., Factor Xa). The typical fusion construct contains a cleavage site that resides in GST fusion partner protein (GST) in conjunction to the above-mentioned consensus sequence (see column 11, lines 31-34). Thus, claim 104 of the instant application is anticipated.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 89 and 96-97 are rejected under 35 U.S.C. 103(a) as being obvious over Vanhoof G. et al. (*FASEB J.* (1995) 9, 736-744) taken with Shimizu M. et al. (*Antimicrob. Agents Chemother.* (1998) 42, 2745-2746).

Vanhoof et al. teach bioactive neuropeptides, which hinder proteolysis and has stabilized bioactivity. One of them, Neuropeptide Y sequence has a "stabilizing" group "Tyr-Pro" at the N-

terminus and a "Pro-Ala" at the C-terminus of Neuropeptide Y (see Table 4 and page 742, the right column, the second paragraph), which meets the limitation set forth in claim 89.

Neuropeptide Y agonists are useful in treatment of anorexia, epilepsy, anxiety, depression, hypertension and heart failure. Thus, Vanhoof et al. meets the claim 97 criteria as neuropeptide Y is used as a therapeutic agent.

Vanhoof et al. does not teach that the neuropeptide can be used as an antimicrobial agent. Shimizu M. et al., however, explicitly teach antimicrobial activity of Neuropeptide Y. Since Vanhoof et al. teach the therapeutic use of Neuropeptide Y (see above statement), it would have been obvious to the ordinary skilled artisan that antimicrobial agents are routinely applied in therapeutic treatments. An antimicrobial activity is one property of neuropeptide Y, since neuropeptide Y has an amphipathic α-helix that is necessary for the antimicrobial activity. The amphipathic α-helix disrupts microbial membrane *via* an electrostatic interaction between the positive charges of the neuropeptide and negative charges of the microbial membrane. Thus, it would have been obvious for the ordinary skilled artisan to combine the above references to successfully arrive at the invention set forth in the application claims 89 and 96-97 as to the therapeutic peptide drug and antimicrobial peptide agent (also note that antimicrobial activity of neuropeptide Y will not be altered by how to use the neuropeptide). Thus, the claimed invention was *prima facie* obvious to make and use at the time it was made.

Claims 89-90, 92-94 and 104 are rejected under 35 U.S.C. 103 (a) as being obvious over Hanafusa, H. et al. (US Pat. No. 5888763) taken with Nishida M. *et al.* (*J. Mol. Biol.* (1998) 281,

135-147), Weiss S. et al. (*J. Viol.* (1995) 69, 4776-4783), and Spurlino J. C. et al. (*J. Biol. Chem.* (1991) 266, 5202-5219).

Hanafusa et al. teach a bioactive peptide "PPPALPPKKN" (see SEQ ID NO:26, column 5) having an N-terminal proline residue in comparison with the consensus sequence "PPALPPKKN"(SEQ ID NO:27) (see Figure 8B) ; thus, the reference meets the limitation set forth in claim 89 "stabilizing group is selected from the group consisting of Pro-, Pro, Pro-Pro-, Xaa-Pro- and Xaa-Pro-Pro-". The peptide is fused to a small stable protein, i.e., glutathione sulfotransferase (GST) (see column 11,lines 39-40, column 24, line 45, and column 25, lines 39-41). The Hanafusa teaching is thus applied to claims 89-90, 92 and 94 of the instant application.

Also, Hanafusa et al. teach that the fusion partner protein serves as a substrate for proteolytic cleavage (e.g., Factor Xa), and that the typical fusion construct contains a cleavage site that resides in GST fusion partner protein (GST) in conjunction to the above-mentioned consensus sequence (see column 11, lines 31-34), which meets the limitation of claim 104 of the instant application.

Hanafusa et al. does not teach that GST protein has four-helix bundle. Nishida et al., however, explicitly teach the crystal structure of glutathione sulfotransferase (from *E.coli*) characterizing a right-handed four helix bundle fold (see Figure 2, page 138) which meets the claim limitation with regard to "four-helix bundle" structural feature of the disclosed protein in claim 93.

It would have been obvious for the ordinary skilled artisan to combine the above references to successfully arrive at the invention of claims 89-90, 92-94 and 104 with regard to the bioactive polypeptide comprising small stable protein, e.g., GST protein, which folding

structure has the characteristic four-helix bundle. The reasons for this are the followings: (i) the proline-rich peptides are fused with GST, as taught by Hanafusa et al. (see Table 1, column 29, and column 30, lines 45-63), (ii) GST protein as a fusion partner has been demonstrated to significantly enhance the *solubility* of the protein fused to GST in the fusion construct, as taught by Weiss et al. (see the right column, page 4776), indicating that GST acts as a "stabilizing protein" in the fusion protein because *solubility* is a criteria of protein stability, (iii) furthermore, GST protein has been shown to have the structural characteristic, i.e., the four helix bundle, as taught by Hanafusa et al., and (iv) also, maltose-binding protein (MBP) has been shown to greatly enhance fusion partner solubility in a fusion protein, as taught by Wagner et al. (see US Pat. No.6329209, from column 23, line 57 to column 24, line 5), and MBP protein has the four helix bundle like structure, as taught by Spurlino et al. (see Figure 2, page 5207). Thus, it would have been obvious for the ordinary skilled artisan to combine the above references to arrive at that the small protein comprising the four helix bundle is a "stabilizing factor and can be employed in constructing fusion protein to produce soluble recombinant product since both GST and MBP proteins enhance solubility of the fusion partner in the fusion construct wherein both GST and MBP have the four helix bundle.

Given the above motivation, one of ordinary skill in the art would have combined the above teachings in order to make and use the bioactive polypeptide comprising the small stable protein having the four helix bundle as well as the proline-rich motif as stated above, which is protease-resistant. Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:30 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703-308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Samuel Wei Liu, Ph.D.

May 15, 2003

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